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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,723	01/04/2001	Ole Kirk	3745.234 US	3358

7590 12/12/2003

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKET (check off ✓) ☐

ATTY:

TMAB DUE 1/26/04

Office Action Summary	Application No.	Applicant(s)	
	09/754,723	KIRK, OLE	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 July 2003*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/295,913.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19*.

4)☐ Interview Summary (PTO-413) Paper No(s). _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

The amendment filed 5-5-03 has been entered into the record. Claims 15-20 are pending and under examination.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The new term "infusion" recited in the claims lacks apparent antecedent basis in the specification as filed. Applicants are specifically cautioned against adding new matter to the disclosure by amendment.

Information Disclosure Statement

The information disclosure filed 7-7-03 has been considered. A initialed copy is enclosed.

It is noted that the "opposition submissions" provided by Applicants are not drawn to the claimed invention and furthermore are not in compliance with either 37 CFR 1.131 or 1.132 and are therefore not dispositive of the issues in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection

The specification lacks written description support for the term "infusion" in the passages pointed out by Applicants to support the amendments to the claims. As such, the term "infusion" is deemed new matter. This issue is best resolved by Applicants pointing to the specification by page and line number where written description support for "infusion" has basis.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Knick et al , in "Bachmann, Lotz, Mchnert (Hsrg)." Insulin/Sulfonylharnstoff. Symp. Munchen 1986, pages 98-106; Karger, Basel 1988).

Knick et al teach the use of the combination therapy of Metformin and Insulin for the treatment of 16 Type II diabetic patients were the insulin was injected and the Metformin taken in tablet form (see bottom page 99 and top of page 103). Insulin is applied under the provision of derivative or analogue of GLP because insulin has a single amino acid in common with GLP and as such the combination of oral metformin and injected insulin as administered to Type II diabetics meets the limitations of the claim.

Claims 15-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Buckley et al (WO 91/11457) in view and Gutniak et al (Diabetologia, 33(suppl):A73, Abstract 246, 1990) of Ramachandran et al (Diabete Metabolisme, 13(2):140-141, 1987) Del Prato et al (The American Journal of Medicine, 90(suppl 6A):6A-77S, 1991) and Parker et al (Diabetes, Volume 40, Suppl 1, Abstract 847) is maintained for reasons made of record and those herein.

Buckley et al teach GLP-1 peptides, 7-34, 7-35, 7-36 and 7-37 and analogs useful for the treatment of Type II diabetes (see the claims, in particular claim 13) in particular. The analogs have amino acid substitutions at positions 7-10 and/or are truncated at the C-terminus and/or contain various other amino acid substitutions in the basic peptide and include amides. These analogs provide for an enhanced capability to stimulate insulin production or exhibit increased stability in plasma as compared to GLP-1(7-37) or both (see pages 29-33, Examples 1 and 2). Buckley et al teach the administration of GLP-1 peptides by injection (see page 28, lines 24-27). Buckley et al differs by not teaching the combination with the oral hypoglycemic agents, metformin.

Gutniak et al teach that th isulinotropic effect of GLP-1 peptides are reproducible *in viva*. Gutniak et al teach that administration to Type II diabetics decreased IMIR, stimulated insulin and inhibits glucagon and somatostatin release.

Ramachandran et al the combination of the oral hypoglycemic agents glibenclamide and metformin is effective in the treatment of Type II diabetes (see paragraph bridging pages 140-141).

Del Prato et al (The American Journal of Medicine, 90(suppl 6A):6A-77S, 1991). Del Prato et al teach that Type II diabetes (non-insulin dependent diabetes mellitus, NIDDM) appears to be a heterogenous disorder characterized by both relative insulin deficiency and impaired insulin action.

Parker et al teaches two insulin secretagogues GLP-1(7-37) and glibenclamide, an oral hypoglycemic agent, when combined had an additive effect on the amount of insulin secretion from HIT cells *in vitro*. Thus, Parker et al broadly teaches the combination of GLP-1 peptides and oral hypoglycemic agents to increase insulin secretion.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer by any appropriate route including injection the GLP-1 peptides, 7-34, 7-35, 7-36 and 7-37 and analogs thereof as taught by Buckley et al and Gutniak et al with the oral hypoglycemic agents such as glibenclamide and metformin of Ramachandran et al to treat Type II diabetes because Parker et al teach that the GLP-1 and glibenclamide when combined had an additive effect on the amount of insulin secretion and therefore the combination of the agents would be reasonably expected to be useful in the treatment of Type II diabetes. One would have been further motivated to combine the GLP-1 with metformin and glibenclamide because Del Prato teach that Type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action and the combination of GLP-1 with the oral hypoglycemic agents would be reasonably expected to further increase the endogenous insulin levels and therefore be useful in the treatment of Type II diabetes and further, one skilled in the

art would have a reasonable exp ctation of success because Gutniak et al that demonstrates that the in *vitro* pharmacology of GLP-1 correlates with the *in vivo* actions.

Applicant's arguments have been carefully considered but are not persuasive. First, Applicants arguments regarding the teachings of Parker et al are noted, however Gutniak et al teach that there is a correlation of in vitro with in vivo results "that the isulinotropic effect of GLP-1 peptides are reproducible *in vivo*". Therefore, the additive effect would be expected *in vivo*. Applicants argue that Parker's experiments were not evaluation of therapeutic potential. This is not persuasive, Parkers experiment clearly used therapeutic agents to investigate the effect of the combination and as such would be seen as such to the skilled artisan. Applicants argue that Del Prato teaches the combination of oral agents with insulin therapy and as such is not dispositive of the combination claimed herein. This is not persuasive, Applicants are arguing teachings not relied upon by the examiner in the rejection. In response to Applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, all agents were known to be useful for the treatment of Type II diabetes, the combination of the agents are well within the skill of the art and motivation for the combination has been specifically articulated. Combination of different agents for the treatment of Type II diabetes were performed in the prior art. Moreover, the courts have held in *In re Kirkhoven* (205 USPQ 1069, CCPA 1980) that "It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form third

composition that is to be used for the very same purpose:idea of combining them flows logically from their having been individually taught in the prior art." Despite arguments to the contrary, this art area (treatment of diabetes) has a tight correlation between *in vitro* test results and *in vivo* results. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants argue that if it was so obvious why did not someone previously perform the combination. This is not persuasive, the fact that the claimed invention was not anticipated by the prior art is not of issue in this application. The fact that some one did not perform an event does not establish that it was not obvious to do so. Applicants argue that since GLP-1 and metformin were known at the time of this application to have overlapping mechanisms of action, that one would not combine drugs that have the same mechanisms. This is not persuasive, as taught by the art drugs that have the same outcomes were used in combined therapy. For example, Riddle (Post Graduate Medicine, 92(2):89-102, 1992) indicates that the long term effect of sulfonylurea is to lower the basal glucose level without much effect on post-prandial levels, and the effect of an evening dose of insulin is also to control the basal glucose level without much effect on post-prandial patterns (page 95, column 2) and as such it is quite evident that the art at the time of filing effectively combined drugs that had the same effect in order to treat type II diabetes. Applicants are drawing conclusions unsupported and contradicted by the art. Further, combining multiple drugs with overlapping mechanisms of action was clearly contemplated and considered by the art "Combined therapy with a sulfonylurea, insulin, and metformin may also prove useful for some patients." (see page 102, column 2). It is noted that GLP-1, as argued by Applicants, stimulates insulin production, a benefit for type II diabetics which are characterized by the art as insulin deficient. It is noted that Applicants argue that GLP-1 at the time of

the invention was an injectable drug and this is provided by the art of Buckley et al as discussed *supra*.

Status of the Claims

All claims stand rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555. The examiner can normally be reached on M-F 9:30pm-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645